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EXPERIMENTAL DATA SERVING AS A BASIS FOR SEPARATE PERMISSIBLE CONCENTRATIONS OF DIBUTYLPHTHALATE

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EXPERIMENTAL DATA SERVING AS A BASIS FOR SEPARATE PERMISSIBLE CONCENTRATIONS OF DIBUTYLPHTHALATE

By

Mincho Spasovski

The manufacture of polyvinylchloride plastic is continually increasing, as is evident from its particularly increased production in the Sodov factory "Karl Marx," near Devnia, Varnensko. The basic structure of polyvinylchloride, reaching to about 50-60% of the general mass of plastic, is composed of plasticizers. For these we primarily employ esters of phthalonic acid / carbobenzoylformic acid, such as dibutyl and dioctylphthalate. The investigations pursued by the chemical engineer T. Ivanov in the preparation of polyvinylchloride show that in the air surrounding the production arrangements, one can find concentrations of fumes of these plasticizers of up to 0.20 mg/l. This presents a problem for analysis, since such concentrations are dangerous to those employed in its production, and there is a lack of separate permissible standards for dibutyl and dioctylphthalate, not only here but abroad. Further, the toxicity of the substances has been poorly studied. Some authors consider the DL_{50} for dibutylphthalate upon rats to be 8 g per kg of weight [10], while others have not established its toxic parameters [7], and yet another group accounts it as quite harmless[8]. The majority are under the impression that dibutylphthalate is not toxic, since the literature does not record symptoms of poisoning connected with the substance [10]. However, this pertains only to oral applications. One notes that when dibutylphthalate is heated, particularly above 140°, the substance turns more toxic and surpasses the toxic plasticizer, trichrysylphosphate [9]. According to some authors, the question of irritation and sensitivity to dibutylphthalate is a matter of dispute [7]. However, it is generally held to be a cause of strong irritation.

Many authors [10, 7] attribute a strong irritability to dibutylphthalate upon respiration, due to the formation of phthalic acid as a consequence of its hydrolysis. An oversensitivity on the part of some persons to dibutylphthalate has been established.

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The Particular Approach

Contemporary requirements for normalization of tolerances for new chemical compounds require two steps to be taken: 1. Reaching a basis for separate permissible standards for concentrations, "PSC," grounded upon experiments with animals; 2. adaptation of the PSC, based on a study of working conditions imposed by the substance and its effect upon the health of personnel.

The task of the present inquiry concerns the first step: the definition of a PSC for dibutylphthalate through experimental approaches.

I. Methodology

1. Hygienic phase: A study of the technological process in the application of dibutylphthalate and a mastery of a method of its detection in the atmosphere.

2. Experimental phase: Investigations employing industrial dibutylphthalate upon white mice, rats, porpoises, and rabbits, to be applied by inhalation, orally, and by using skin and grooming reflexes.

The inhalatory device is composed of a 10 liter container in which the experimental animals are placed [6]. The dibutylphthalate is heated to a temperature of 140-200° by means of a small boiler with a contact thermometer, so that its fumes pervade the container with the help of a vacuum pump. The desired concentrations are metered through both chemical and instrumental means. The discrimination between both conditions is graded by a 2 to 300 pointer (reading) device.

The following indicators were concentrated upon: mortality, weight, weight coefficient of liver and kidneys, clinical chart, hematological chart with an account of Eo cells and of DD, blood sugar, cholinesterase activity, catalyzing activity, Beltychin fractions, fatiguing (by swimming tests to death), motor activity (this was done with the help of a measuring device monitoring the activity of the mice), and conditioned reflex responses by Golubev's method [1, 6].

3. The statistical phase: All results were processed to arrive at a standard deviation for the average and its reliability in the comparison of experimental and control animals.

II. Physico-Chemical Characteristics and Applications

Dibutylphthalate is a dibutyl ester of phthalic acid, $C_6H_4(COOC_4H_9)$, with a molecular weight of 278.34. It results from a reaction of phthalic anhydride (phthalandione) with butyl alcohol. It appears as a colorless, involatile,

inflammable liquid with an average inflammability of t.k. 340°, and t.t. 315°, with a viscosity of 1.042 to 1.050. The industrial product, which we used, contained 98% dibutylphthalate with an acid number of 0.3. Dibutylphthalate is employed as a softener for the polyvinylchloride plastic. To that end, it is added to the polyvinylchloride resin and heated to a temperature of 140-170°. After this, the resultant plastic undergoes the following operations: extrusion, compression, and joining at a temperature range of 160-240°.

III. Identification of the Toxic Parameters of Dibutylphthalate

1. Determination of Fatal Dosages

The white rats of a group of ten and a group of four porpoises received orally 5, 10, 15, 20, and 50 (50: only the porpoises) g/kg of body weight dibutylphthalate. Not one of the animals perished, during an interval of 10 days. No pathological indications were apparent for the selected set of indicators. Fatal doses can not be identified, since the animals do not absorb large quantities of the substance. This would show the weak toxicity of dibutylphthalate when applied orally.

2. Determination of Fatal Concentrations

54 white mice survived concentrations of dibutylphthalate of 0.17 to 0.40 mg/l of atmosphere. At concentrations of 0.43 to 0.61 mg/l only one of 22 mice died. At concentrations of 0.70 to 0.93 mg/l, of 18 subject animals, 9 died, and at a concentration of 1.9 mg/l, all mice died.

3. Identification of Threshold Concentrations

30 white mice, during a period of about 2 months, were trained and conditioned to a reflex coupling electric shock with a (sounding) bell. After this, we subjected conditioned mice to 6 hours of various concentrations of dibutylphthalate and studied the change in their reflexes. We established that at concentrations of 1.9 mg/l all animals perished in an interval of 3 days. At concentrations of 0.46 mg/l, only one of three such animals reacted to the poison, during the second day of the latency period for the reflex, and of shock. At concentrations of 0.26-0.36 mg/l, no reliable deviations for such reflexes were apparent between experimental or control animals: $M_c - M_o = 3 < 17.7$. On this basis, the threshold concentration of dibutylphthalate appears to be at 0.30 mg/l atmosphere.

IV. Toxicity of Dibutylphthalate in Repeated Application

Eight rats were treated by inhalatory means with an average concentration of 25 mg/l with a range of 0.19 to 0.36 mg/l of the compound in the atmosphere. A second set of eight were treated orally with a single dose comprising 20 g/kg of weight. As a result, within a week, the animals of these two groups perished at a general massive concentration of 0.46 to 2.31 mg/l and a general massive dose of 20 to 120 g/kg of weight.

Six porpoises were treated daily per os with 5 g/kg of weight. The animals expired with a general massive dosage of 10 to 20 g/kg of weight.

Two rabbits ingested daily 2 g/kg of body weight of dibutylphthalate. As a result, the rabbits died within 2 weeks, with a general massive dose of 28 to 30 g/kg of weight. The tails of five rats were moistened with dibutylphthalate for a period of 4 months. The animals increased in weight with no noticeable pathological indications.

The cumulative coefficient is the relation between the total dosage or concentration, which is ruinous in effect upon half or all the animals, and the corresponding absolute dosage or concentration. An absolutely lethal concentration for rats is defined as 2.7 mg/l of atmosphere. With supplementary action of 1/10 the concentration, rats perish at a general massive concentration of 0.46 to 2.31 mg/l; thus, the cumulative coefficient is a little less than 1. With a single oral application of dibutylphthalate in a dose of 20 g/kg of weight, no animal dies, while with several applications of 5 g/kg of weight of the substance, porpoises die at a general massive dosage of 20 g/kg of weight. This demonstrates that oral application of dibutylphthalate has a cumulative coefficient of slightly less than 1. Such data indicate the high cumulative characteristics of dibutylphthalate and its effect upon the reactions of oversensitivity known to be connected with it.

VI. [sic] Study of Chronic Exposure to Dibutylphthalate

To establish the chronic effect of dibutylphthalate, we subjected 15 white mice to inhalation procedures for 6 hours daily, for a period of 93 days, using 15 mice for control. Armed with some idea of the strong cumulative effect of dibutylphthalate, we used concentrations that were 1/5 to 1/10 less than that identified as a threshold dose: 0.30 mg/l. The container chamber received the following concentrations: for a period of 11 days, 0.085 to 0.078 mg/l; for 15 days, 0.061 to 0.040 mg/l; for 60 days, 0.040 to 0.017 mg/l. Six days before the cessation of treatment, we purposely increased concentrations which were close to that established as the threshold (0.17 to 0.42 mg/l of atmosphere), for the purpose of placing the animals under a heavy charge and for the strongest effect of dibutylphthalate.

With an increase in poisoning, we arrived at these results:

1. With regard to reflexes: The experimental animals showed, in the last 10 days, a 68.5% rate of positive response to 401 events, while the control animals showed a 73% rate to 348 events. Proceeding arithmetically to establish reliability, we determined that $M_c - M_o = 5.5$, which figure is significantly smaller than that established for absolute reliability (9.93), but it approaches a probability correlation of 6.62. Consequently, the deviation arrived at by arithmetical averages for the experimental and control mice can not be taken as trustworthy and might be due to accidental exceptions (random influences).

With regard to differentiations: All the experimental animals show a 73% rate in response to events, while all the control animals show an 85.4% rate. For establishing reliability, this difference can be taken as absolutely reliable: $M_c - M_o = 13.6 > 6.18$.

2. The latency period for the reflexes of experimental animals can be expressed as an arithmetical average of 0.63 sec, while the control averaged 0.52 sec. These figures show the data not to be within the limits of absolute or probable reliability $M_c - M_o = 0.11 < 0.93$.

3. The weight coefficient: It appears that this coefficient for liver and kidneys is one and the same both for control and experimental animals. The coefficient for liver for both groups of mice is 1.69. The average coefficient for kidneys for experimental mice is 5.7 and for the controls is 5.6.

4. Weight among experimental mice shows a gain for three, a loss for two, and no change for three. The control group shows three cases of increase, two of decrease, and two of no change in weight.

5. Motor activity appears slightly increased for the experimental animals. In the day following dosing, the experimental mice showed an average activity level of 163 and the controls of 154. Still, this difference does not fall within the limits of reliability.

6. Fatiguing is measured by the interval of time it takes for the animals to begin to swim in a basin until the time they drown. Two animals, one of the experimental and the other of the control group swam for more than 5 hours. The remaining five of the experimental group swam for intervals of 75 to 330 min, or for an average of 208 min. The other four mice of the control group swam for intervals of 60 to 260 min, or for an average of 151 min.

7. During the time of the experiment, seven experimental mice, and eight control mice sickened. All such were segregated and destroyed.

The results of the study of chronic exposure show that there is a lack of reliable deviations between experimental and control mice for the selected indicators, such that one can say that they are influenced by dibutylphthalate activity. Whatever differences may exist show reliable indications of an obvious lowering of endurance in the exposed mice. Accordingly, the continuing action of fumes heated above 140° of industrial dibutylphthalate in average concentrations of 0.037 mg/l with tolerances ~~of 0.017~~ to 0.085 mg/l do not predispose to pathological manifestations in observed intervals for other indicators in the exposed animals.

VII. Establishing Separate Permissible Standards for Dibutylphthalate Concentrations

The basic method for establishing temporary separate permissible standards for concentrations of given substances rests upon results obtained from

experiments with animals. As auxiliary methods for defining the PSC, one can use analogy and statistical reworking of physico-chemical data [2, 5].

1. Identification of a PSC Based on Animal Experiments

The identification of a PSC for a given substance is accomplished by use of a concentration which can be employed in an experiment simulating chronic exposure and which can be decreased by a known coefficient to a security scale ranging from 10 to 100. Such a coefficient ought to increase in direct dependence upon the following circumstances for the said substance: a) a narrow range of strong influence, the relation of LD_{50} to a threshold concentration; b) presence of skin absorption activity; c) strong cumulative effects; and d) the existence of high volatility.

We establish chronic exposure to dibutylphthalate to be at an average of 0.037 mg/l.

The zone of toxic effect of this substance is very narrow: The average deadly concentration, LD_{50}, is 0.80 mg/l and is quite close to the threshold concentration of 0.30 mg/l. We have established that dibutylphthalate is a strongly cumulative poison with a cumulative coefficient of slightly less than 1.

At ordinary temperatures, dibutylphthalate is somewhat weakly volatile. However, at temperatures of 140 to 170°, which are common to its production uses, its volatility and toxicity are singularly high. The skin absorptive capacity of dibutylphthalate is not established.

Based upon the findings that dibutylphthalate has a narrow zone of concentrated effect, we maintain that in cases of persistent exposure, concentrations be lowered to 1/3, from 0.037 to 0.017 mg/l. Bearing in mind the strongly cumulative nature of dibutylphthalate, we consider the later concentration figure should best be lowered by at least 10 times, or that the cumulative coefficient for personnel safety be 30 on the scale.

Considering all present data, we determine that for fumes and aerosols, employed in a heated state beyond 140° of dibutylphthalate, the separate permissible standard for concentration be at 0.001 mg/l of atmosphere.

2. Establishing a PSC Based on Research

The PSC for dibutylphthalate is defined by formulas suggested by Lyubin [5] and other Soviet authors upon the basis of the particular toxic parameters and the physico-chemical data defining its properties.

The following results are derived:

a. By the formula, log PSC = log K - 1.1 + log M, where K is the defined threshold concentration and M is the molecular weight, the PSC for dibutylphthalate becomes 0.024 mg/l of atmosphere.

b. By the formula log PSC = 0.91 log LD_{50} - 2.7 + log M, the PSC becomes 0.0003 mg/l.

c. By the formula log PSC = -0.016M - 1.8 + log M, the PSC becomes 0.00013 mg/l.

3. Defining the PSC by Analogy

The closest substance to dibutylphthalate in chemical structure and physico-chemical properties is phthalic anhydride. The PSC of the anhydride is established by the Soviet toxicologists Kremneva and Tolska [3] at 0.003 mg/l of atmosphere. However, remembering the particularly narrow zone of toxic effect of dibutylphthalate, we propose a three times lower concentration than that for the anhydride, which would be 0.001 mg/l.

Analysis of the given permissible standards defined by the above methods makes clear that differences in the PSCs rest upon physico-chemical indicators. Based on animal experiments, our particular standard, defined as 0.001 mg/l, is ten times lower than that resulting from formula (a), and three or seven times higher than those from formulas (b) or (c). However, the formulas do not account for the strong cumulative effect of dibutylphthalate, and further, its skin absorptive capabilities are unknown. Therefore, we hold that a more correct temporary separate permissible standard of concentration for industrial dibutylphthalate be set at 0.001 mg/l of atmosphere.

Conclusions:

1. Based on experiments using animals (108 mice, 140 rats, 48 porpoises, and 3 rabbits) subjected to single and multiple inhalatory, oral and skin-coating dosages, and which are supported by mathematical and analogical methods, the separate permissible standard for concentrations of industrial dibutylphthalate heated above 140° is 0.001 mg/l of atmosphere.

2. The toxicity of dibutylphthalate depends upon the modality of its introduction to the organism. Most toxic are its fumes heated above 140° which penetrate and consume the lungs. The substance is weakly toxic in oral application. It does not possess skin absorptive capability.

3. Dibutylphthalate possesses a highly cumulative effect in inhalation and ingestion. The cumulative coefficient falls just short of 1, which explains the hypersensitivity associated with it.

[Note: No bibliography appended to this article, even though references were cited in it.]